REMOVAL OF DEPOSITED ^{238}Pu, ^{239}Pu AND ^{241}Am BY PROLONGED ORAL INTAKE OF DTPA

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Oral treatment with chelating agents would be the most convenient method for the removal of incorporated actinides from the body, especially in cases where protracted administration is indicated. There has been, however, a general assumption that DTPA, the present agent of choice, would be ineffective when given orally because of the low rate of intestinal absorption.

In a previous paper it was shown that after a prolonged addition of Zn-DTPA to drinking water substantial fractions of Pu-239 were removed from the rat skeleton and liver (Taylor D.M. and Volf V., Health Phys. 38, 147-158, 1980). The aim of the present investigation was to collect further experimental data to support the hypothesis that prolonged administration of quite small amounts of DTPA represents a true alternative to the hitherto accepted schedule of repeated DTPA injections.

In the first experiment on female Heiligenberg rats (Tab.1) the effects of various concentrations of Zn-DTPA in drinking water on the retention of Pu-238 and Pu-239 were compared with the effect of Ca-DTPA injected in human equivalent doses (1g Ca-DTPA in a 70kg man). After Ca-DTPA injections the contents of both isotopes in the bone and liver were reduced by about 40% and 70%, respectively. A similar effect was achieved with Pu-238 and Pu-239 by drinking 10^{-4} and 10^{-3} molar Zn-DTPA, respectively. Thus, the effect of oral Zn-DTPA was substantially more pronounced with Pu-238 than with Pu-239, both in the bone and liver. This suggests that with low chelate concentrations in the tissues following oral administration of DTPA the mass of Pu becomes a critical factor: For equal activities the mass of Pu-238 is about 280 times less than that of Pu-239.

The total DTPA intake in rats drinking Zn-DTPA was between 1 and 30 times higher than in those injected with Ca-DTPA yet it proved equally effective in reducing the contents of Pu-238 in the bone and liver, respectively. The effect in the liver of oral DTPA can be easily understood when assuming that only about 3% of ingested DTPA is absorbed from the intestine. In the bone, however, it is obviously important that a low level of DTPA is maintained for longer periods of time, thus preventing the redeposition of the small quantities of Pu-238 released. The higher mass of released Pu-239 can be bound only if about 30 times higher local DTPA concentrations are achieved.

In man, chelation therapy is indicated after incorporation of substantially lower amounts of Pu-239 than are those usually administered in animal experiments (e.g., the activity injected in the above experiment was 7μCi per 70kg body weight). Thus, animal studies with the low mass Pu-238 seem to be a suitable model for human accidental incorporation of Pu-239.

In the second experiment (Tab.2), Zn-DTPA was added to drinking water so that the intake equalled approximately 300μmoles per kg body weight per day, i.e. 10 x the human equivalent dose. Male Sprague-

Dawley rats were injected with Pu-238 and Am-241 citrate, 4d or 30d before the beginning of treatment which was continued until 105d,when the animals were sacrificed. The two actinides were administered simultaneously in order to compare their response to treatment under identical conditions. The changes in the overall retention of Am-241 in vivo were followed by repeated whole body counting.

At 15 weeks postinjection the whole body retention of Am-241 as well as the content of Pu-239 and Am-241 in the skeleton were reduced to approximately 60% and 40% by the treatment with Zn-DTPA beginning late or early after injection of the actinides, respectively. In the soft tissues, both Zn-DTPA treatments reduced the Pu-238 content to below the detection limit, and that of Am-241 to about 10% and 50% in the liver and kidneys, respectively.

The latter results indicate that substantial fractions of Pu-238 and Am-241 can be removed even by delayed administration of DTPA in drinking water, except for a small fraction of Am-241 which remains fixed in the kidney, even if DTPA treatment begins only 4 d after Am-241 injection.

It is at present not clear what happens to the Zn-DTPA introduced into the gastrointestinal tract. The acid stomach juice may lower the stability of the chelate, while during the neutralization process in the small intestine the previously freed DTPA may bind Zn as well as Ca, Fe and other metals, from food and/or from the gut mucosa. All this could result in a greater oral Zn-DTPA toxicity than that expected from the injection studies on the relative toxicity of Ca- and Zn-DTPA. However, as shown previously (see above), there was no evidence of impaired intestinal DNA synthesis or iron utilization in rats exposed to up to $3x10^{-2}$ molar Zn-DTPA in drinking water for 21d. The total amount of Zn-DTPA given in this toxicity study was about twice the highest amount administered in the present experiments.

As seen in Table 3, initial uptake of Pu-238 and Am-241 in the distal half of the femur was twice as high as that in the proximal half. The subsequent release of the two actinides from the distal half was more pronounced than that from the proximal one. Thus, the distal: proximal content ratio decreased with time, especially after treatment; this decrease appeared earlier with Am-241 than with Pu-238. The latter suggests slight differences in binding of the two actinides in the long bones.

In conclusion, the results obtained indicate a surprisingly good effect on the retention of Pu-238 and Am-241 of protracted treatment using small amounts of Zn-DTPA in drinking water, even when treatment was started as late as one month after actinide injection. The total amounts of Zn-DTPA used in the present study were equal to only one half or less of those shown previously to be non-toxic.

TABLE 1. RETENTION OF ACTINIDES IN FEMALE HEILIGENBERG RATS AS INFLUENCED BY DTPA

Treatment			Actinide content (% of injected amount; arithm.means + S.E.)			
			Skeleton		Liver	
Substance	Concn. or amount	Total amount (mmol / kg)	Pu-238	Pu-239	Pu-238	Pu-239
Controls 4d	–	–	63.9 ± 4.1	65.8 ± 2.3	19.2 ± 1.7	20.9 ± 1.0
Controls 28d	–	–	54.1 ± 1.3	61.7 ± 1.9	4.1 ± 0.2	4.6 ± 0.4
Zn-DTPA (Drinking-water)	$1x10^{-4}$ M	0.09	40.8* ± 1.3	59.5 ± 2.6	2.9* ± 0.2	4.5 ± 0.6
	$3x10^{-4}$ M	0.27	35.2* ± 1.3	56.6 ± 2.9	2.2* ± 0.1	3.7 ± 0.3
	$1x10^{-3}$ M	0.90	32.6* ± 0.9	54.2* ± 3.0	1.9* ± 0.2	3.4* ± 0.3
	$3x10^{-3}$ M	2.70	30.5* ± 1.5	49.5* ± 2.8	1.8* ± 0.1	1.9* ± 0.1
	$1x10^{-2}$ M	9.00	30.9* ± 1.8	39.4* ± 2.9	1.2* ± 0.1	1.1* ± 0.1
	$3x10^{-2}$ M	27.00	31.4* ± 1.4	27.7* ± 2.6	1.0* ± 0.1	0.6 ± 0.1
Ca-DTPA (s.c.in-jection)	30 µmol/kg	0.27	34.2* ± 1.2	37.7* ± 2.9	1.4* ± 0.1	1.2* ± 0.1

Treatment started 4d after i.v.injection of Pu-citrate (0.1µCi/kg) and continued 3 x per week for 3 weeks. Rats (5-10 per group) sacrificed 4 weeks post Pu.

* Statistically significant difference between control and treated group ($p < 0.05$) (t-test).

TABLE 2. RETENTION OF ACTINIDES IN MALE SPRAGUE DAWLEY RATS AFTER DRINKING Zn-DTPA

Group (Time post injection)		Actinide content (% of injected amount; arithmetic means ± S.E.)					
		Skeleton		Liver		Kidneys	
		Pu	Am	Pu	Am	Pu	Am
Controls	4d	51.9 ± 1.1	39.4 ± 1.0	13.5 ± 0.7	33.0 ± 1.7	1.9 ± 0.1	2.3 ± 0.1
Controls	105d	51.6 ± 1.0	36.9 ± 1.0	0.7 ± 0.2	1.3 ± 0.5	0.2 ± 0.03	1.0 ± 0.1
Late DTPA	105d	32.9 ± 1.6	23.5 ± 1.0	< 0.2	0.1 ± 0.01	< 0.03	0.6 ± 0.1
Early DTPA	105d	21.9 ± 0.6	14.3 ± 0.4	< 0.2	0.1 ± 0.01	< 0.03	0.5 ± 0.1

Zn-DTPA was added to drinking water (concentration: 3×10^{-3} molar) from day 4 (early DTPA) or day 30 (late DTPA) up to day 105 after i.v.injection of 0.5μCi/kg of Pu-238 and Am-241 citrate.

TABLE 3. EFFECT OF ORAL Zn-DTPA ON THE RETENTION OF ACTINIDES IN THE FEMUR OF SPRAGUE-DAWLEY RATS

Group (Time post injection)		Actinide content (% of injected amount; arithmetic means + S.E.)					
		Distal half		Proximal half		Distal/Proximal Ratio	
		Pu	Am	Pu	Am	Pu	Am
Controls	4d	1.75±0.06	1.28±0.03	0.90±0.05	0.67±0.04	1.98±0.15	1.93±0.11
Controls	105d	1.61±0.04	1.09±0.04	0.96±0.03	0.76±0.02	1.68±0.06	1.43±0.05
Late DTPA	105d	0.99±0.04	0.62±0.03	0.66±0.04	0.55±0.03	1.50±0.03	1.14±0.07
Early DTPA	105d	0.58±0.03	0.38±0.01	0.51±0.02	0.34±0.01	1.16±0.10	1.13±0.05

For explanations see Table 2.